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FEASIBILITY STUDY: A DEVICE TO INFUSE HYPERTONIC SOLUTIONS INTO BONE MARROW

Final Report

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Robert A. Gunther, Ph.D.

George C. Kramer, Ph.D.

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Departments of Surgery and Human Physiology
School of Medicine
University of California
Davis, CA 95616

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19. ABSTRACT The development of small volume resuscitation formulations makes intraosseous infusion an attractive alternative to intravenous cannulations. We performed studies to evaluate the feasibility of developing a device which would allow military corpsmen to rapidly, safely and effectively infuse hypertonic saline/ dextran solution into bone marrow. The following results are from studies with unanesthetized and anesthetized sheep or cadavers. A 2-4 minute intraosseous infusion of 200 ml of 7.5% NaCl/6% dextran 70 (HSD) can effectively resuscitate hemorrhaged sheep. Intraosseous infusion of isotonic fluid for treatment of significant hemorrhage is impractical because of the excessive time or pressure required to deliver adequate volumes; however, effective volume expansion can be achieved with a 2-4 min, syringe-delivered small volume (4 ml/kg) of hypertonic saline dextran. From the study of plastic cast resulting from the injection of Bateson's medium into the sternum of sheep or cadavers, we conclude that intraosseous infusion into the sternum provides direct vascular access via the thoracic veins in both man and sheep. No functional or histological evidence of pulmonary embolism from marrow tissue was found in sheep following rapid intraosseous infusions of HSD. A prototype device which installs onto the midline of the manubrium or sternal body was designed and constructed to deliver low volume, concentrated saline/dextran solutions into the red bone marrow.

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FOREWORD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 86-23, Revised 1985).

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SUMMARY

1. A 2-4 minute intraosseous infusion of 200 ml of 7.5% NaCl/6% dextran 70 (HSD) can effectively resuscitate hemorrhaged sheep.

2. Intraosseous infusion of isotonic fluid for treatment of significant hemorrhage is impractical because of the excessive time or pressure required to deliver adequate volumes; however, effective volume expansion can be achieved with a 2-4 min, syringe-delivered small volume (4 ml/kg) of hypertonic saline dextran.

3. From the study of plastic cast resulting from the injection of Bateson's medium into the sternum of sheep or cadavers, we conclude that intraosseous infusion into the sternum provides direct vascular access via the thoracic veins in both man and sheep.

4. No functional or histological evidence of pulmonary embolism from marrow tissue was found in sheep following rapid intraosseous infusions of HSD.

5. A prototype device which installs onto the midline of the manubrium or sternal body was designed and constructed to deliver low volume, concentrated saline/dextran solutions into the red bone marrow.

SPECIFIC AIMS

Animal investigations in our lab (1,2,3,4) and those of others (5,6,7,8) have established that small volume infusions of hypertonic saline can effectively restore cardiovascular function after hypovolemic shock. The development of small volume resuscitation formulations makes intraosseous infusion an attractive alternative to intravenous cannulations. We are performing a feability study to evaluate the possible development of a device which would allow military corpsmen to rapidly, safely and effectively infuse hypertonic saline/dextran solution into bone marrow. This device would shorten the time delay normally experienced in gaining intravenous vascular access with catheters. Our overall aim of this contract is to perform the initial engineering studies to determine the design specifications required for development of an effective bone marrow infusion device. Specific aims of this one year feasibility study are:

1) Preliminary evaluation of the efficacy and safety of intraosseous HSD resuscitation of hemorrhage using a bone marrow needle.

2) Determine the anatomical variability of possible infusion sites and the pressure-flow relationships of different resuscitation solutions infused into different bone marrow sites.

3) Perform initial evaluations of any pathological effects of intraosseous infusion of hypertonic formulations.

4) Develop a prototype injection device which allows intraosseous infusion of 50-250 ml of hypertonic saline dextran over 2-5 minutes.

RESEARCH SUMMARY

Our research on hypertonic saline dextran (HSD) resuscitation and intraosseous resuscitation has resulted in 1 published manuscript and 5 published abstracts. The following is a summary of our work which is organized to relate directly to the numbered specific aims listed on the previous page for contract DAMD-17-88-C-8127.

1. Efficacy of intraosseous resuscitation with HSD (published manuscript M1, abstract A1)

Infusion of 250 ml of 7.5% NaCl Dextran 70 (HSD) is an effective treatment of hypovolemia in trauma patients. However, the significant time delay associated with establishment of intravenous access may limit the usefulness of pre-hospital resuscitation with HSD. Infusion directly into red bone marrow is a rapid means to achieve intravascular access. In this study, we examined the cardiovascular response to a 2 hr hemorrhage (shed blood volume = 38 ± 7 ml/kg) and resuscitation by a 2 min infusion of 200 ml of HSD directly into the sternal marrow of 6 unanesthetized sheep: six control sheep were resuscitated with i.v. HSD. Mean results ± SD are shown for mean arterial pressure (AP). Cardiac output (CO) and plasma sodium ([Na]) in figure 1.

All sheep were long term survivors, 7+ days. Histological sections of injection sites showed no significant pathology. We conclude that effective resuscitation with hypertonic saline dextran can be accomplished via intraosseous infusion.

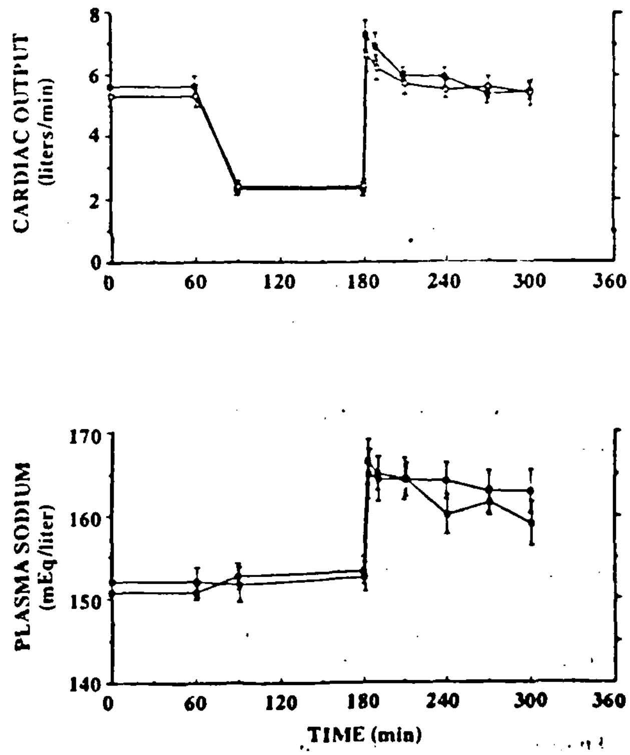

Figure 1 - Mean (± SEM) cardiac output and plasma sodium in hemorrhaged sheep resuscitated with 200 ml of hypertonic saline/dextran administered by intraosseous infusion (-■-) and peripheral vein infusion (-□-).

2. Anatomical variation and pressure flow relationships of intraosseous resuscitation (published abstracts A2 and A3).

Intraosseous injections (IOI) of 7.5% NaCl/6% Dextran (HSD) have been proposed as a rapid means of gaining vascular access and delivering fluids to hypovolemic patients. In the present study, Batson's medium was injected into the sternums of sheep

that had been hemorrhaged, resuscitated with IOI of HSD via bone marrow needle, and sacrificed with pentobarbital overdose. The injection of 100-200 ml of Batson's medium was made using a 13 gauge needle at the same site used for the IOI. After the bone and soft tissue were macerated, the resulting plastic cast demonstrated the vascular route of sternal IOI. Batson medium filled the marrow for 3-8 cm around the needle and both of the internal thoracic veins. In order to assess the feasibility of doing similar IOI of HSD in hypovolemic patients, studies of human cadaveric sternums were conducted that were similar to those done in the sheep. The sternums were obtained from either embalmed or unembalmed cadavers and injected with Batson's injection medium in the median plane opposite the third intercostal space. The casts obtained from these studies demonstrated the same vascular route in the human that was described above for the sheep. In addition, the sternums of six cadavers were sectioned in the horizontal plane and the dimensions of the marrow space were measured. At the second and third intercostal spaces the dimensions of the marrow space ranged from 26-31 mm laterally and 6-11 mm anteroposteriorly. The cortical bone ranged from 1.5-2.5 mm in thickness. In conclusion, intraosseous infusion into the sternum provides direct vascular access via the thoracic veins in both man and sheep.

Because the practical limitation of intraosseous infusion of resuscitation fluids apepars to be the rate of fluidi delivery, we examined the pressure-flow relationship of intraosseous infusions. Six anesthetized sheep each had its sternum punctured with a 14 gauge needle which was connected to a Harvard infusion pump. Fluids infused were 0.9% NaCl; 7.5% NaCl/6% dextran 70 and a near saturated, viscous 25% NaCl/24% dextran solution. Infusion rates were varied from 5-70 ml/min, while driving pressures were measured from a side port. Pressures produced at the same flow rate were affected by slight movement of needle position, but at each position a linear pressure flow curve could be generated.

Table 1 shows the time required to deliver an effective volume of each fluid at different driving pressures.

Time to Deliver Resuscitation Volume

Solution	Dose	100 mm Hg	300 mm Hg	1000 mm Hg
Normal Saline	2000 ml	210 min.	70 min.	21 min.
7.5% NaCl 6% Dex	250 ml	36.5 min.	12.2 min.	3.7 min.
25% NaCl 24% Dex	50 ml	15.2 min.	5.1 min.	1.5 min.

Pressures generated by gravity flow (~100 mm Hg) or i.v. pressure bag (~300 mm Hg) are inadequate to deliver resuscitation fluid into the bone marrow at the rapid rates required by trauma patients. Intraosseous infusion of isotonic fluid for treatment of significant hemorrhage is impractical because of the excessive time or pressure required to deliver the large volumes required for adequate volume expansion. Effective volume

expansion can be achieved with a 2-4 min, syringe-delivered small volume (4 ml/kg) of hypertonic saline dextran.

3. Initial evaluation of pathological effects of intraosseous infusion (published abstract A4)

In previous studies, we demonstrated equivalent cardiovascular responses to resuscitation of hemorrhaged sheep with 7.5% NaCl/6% dextran 70 (HSD) infused either IO or IV. However, the usefulness of intraosseous resuscitation would be limited by significant bone marrow pathology or pulmonary embolism from marrow tissue. Ten awake sheep were subjected to 2 hrs of hemorrhagic hypotension (arterial pressure - 50 mm Hg, bled volume - 1.2-1.8 liters), and then resuscitated with a 200 ml IO infusion (2-4 min) of HSD via bone marrow needle. Cardiovascular function was normalized one min after infusion. No sheep showed any deleterious effect from the infusion on either blood gases or respiratory rate. All sheep survived in apparent good health until euthanasia after 1-2 d (n=5); 2 wks (n=2); or 6 wks (n=3). Histological examination of sternums showed that the bony trabeculae and marrow fat remained intact, but hemopoietic cells exhibited a focal washout in the vicinity of the infusion site at 1-2 d post infusion. Specimens from the injection sites after 2-6 wks show replacement of hypocellular areas with fibrous tissue. In all cases, these changes were confined to the injection sites and in no case were they greater than 0.6 cm in diameter. No functional or histological evidence for pulmonary embolism was found.

4. Prototype intraosseous infusion device (published abstract A5)

We have produced 10 prototype intraosseous infusion devices for trials in sheep, pig and human cadavers. Two prototypes have been delivered to the Letterman Army Institute of Research for their experimental evaluation. Engineering design principles were applied to the problem of delivering low volume, concentrated saline/dextran solutions into red bone marrow for field treatment of hypovolemic shock. Special consideration was given to the field environment, the need for speed and safety, and the range of normal anatomic variation. This led to the development of a device (figure 2) that installs onto the midline of the manubrium or sternal body and delivers fluid into the marrow circulation. Automatic adjustment for variations in tissue and bone thickness is incorporated into the device. Minimal training appears necessary to properly use the device. An experienced technician can install the device and begin infusion in less than 30 seconds utilizing easily palpable landmarks. Design refinements have been based on prototype testing in human cadavers and anesthetized sheep.

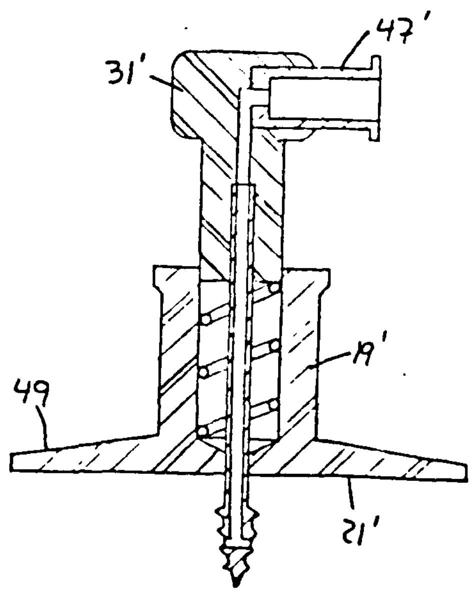

Figure 2.

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List of Publications

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Manuscripts:

M1. Kramer, G.C., J.C. Walsh, P.R. Perron, R.A. Gunther, S. Mertens, J.W. Holcroft, and F.W. Blaisdell. Resuscitation of hemorrhage with intraosseous infusion of hypertonic saline dextran. Brazilian Journal of Medical and Biological Research 22:283-286, 1989.

Abstracts:

A1. Kramer, G.C., J.C. Walsh, P.R. Perron, R.A. Gunther, S. Mertens, J.W. Holcroft and W.F. Blaisdell. Resuscitation of hemorrhage with intraosseous infusion of hypertonic saline dextran. FASEB Journal 2:A974, 1988.

A2. Perron, P.R., R.A. Gunther and G.C. Kramer. Pressure-flow relationships of intraosseous infusions. Circulatory Shock 24:282, 1988.

A3. Saavedra, J., H.A. Patterson and G.C. Kramer. Intraosseous injection of hypertonic saline dextran: Anatomic considerations in man and sheep. Circulatory Shock 24:283, 1988.

A4. Kramer, G.C., S.C. Mertens, L. Halvorsen, J.W. Holcroft, P.R. Perron and R.A. Gunther. Intraosseous infusion of hypertonic saline dextran: effects on pulmonary function and the histology of bone marrow. Circulatory Shock 27:348, 1989.

A5. Bay, B.K., J.M. Henderson, F.W. Blaisdell, and G.C. Kramer. A device for rapid vascular access to the sternal marrow spaces for delivery of resuscitation fluids. Circulatory Shock 27:344-345, 1989.